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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,803	02/05/2001	Vanitha Ramakrishnan	044481-5044	3916

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Intellectual Property Group
MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,803	RAMAKRISHNAN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/16/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are pending examination.

The applicants' traversal, the amendment to claims 1, 5, 10, 15, 21, 23, 28-30, the cancellation of claims 2, 6, 7, 9, 11, 12, 14, 16-20, 22, and 25 in paper no. filed on 9/16/03 is acknowledged and considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification recites that the invention features a genus of transgenic mice comprising either a non-functional GPV gene or a modified GPV gene and goes on to contemplate that there are techniques for producing the transgenic mice (pages 5-13). The specification requires that the starting material, which is a nucleic acid encoding a GPV polypeptide, be used in a method of making a transgenic non-human mammal comprising either a modified or a non-functional GPV gene. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (page 12). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) The DNA sequence encoding GPV comprising a coding region of mouse GPV (including the putative initiator Met to Leu^{389}) was replaced by a neo cassette and injected the vector into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the disclosure provides characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the specification displays the GP V-/- mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (page 23-24). The specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (pages 25).

However, the art of record teaches a GPV-deficient mouse whose platelets have undiminished thrombin responsiveness and does not exhibit a Bernard-Soulier phenotype

(Kahn et al., page 4112, cited on a previous PTO-892). Kahn produces GPV-deficient mice using gene targeting, wherein the entire GPV gene was knock out. The mice responded normally to thrombin and the tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115). The platelets from GPV-deficient mice responded to 1nmol/L thrombin like wild type mouse (page 4115). In addition, the art of record for GP V teaches that the role of GP V is poorly defined (IDS, Dong, pages 4355 and 4362).

In view of the claims lacking essential materials and methods (e.g., targeting construct used), one skilled in the art would not be enabled to produce a transgenic mouse as set forth in the claimed invention without an undue amount of experimentation because the claims do not distinguish the mouse taught by Kahn and the mouse taught by the specification. The conflicting phenotypes displays that the art of transgenic is not predictable art with respect to modifying a gene in a mouse and reasonably predicting the resulting phenotype from the modification. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mouse comprising a modified gene (e.g. GPV gene), it is not predictable if the modified gene would result in a particular phenotype. [Note that although the claimed transgenic mouse is not limited to modified expression of the GPV protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest

interpretation of the claimed transgenic mouse having cells, which has a modified GP V protein, wherein the modified protein demonstrates a reduced functionality to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mouse would serve if the reduced functionality is not at a sufficient level for a resulting phenotype).]

In conclusion, in view of In Re Wands Factors, the claimed invention is not considered enabled. Furthermore, without reciting the essential materials and methods, in particular when the modification of the GP V gene must occur at a level resulting in a corresponding phenotype that would distinguished it from the mouse taught by Khan; the unpredictability of the art with respect to modified gene behavior in transgenic mouse; and the breadth of the claims drawn to any transgenic mouse whose genome has a modified GPV gene, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants' arguments filed 9/16/03 have been fully considered but they are not persuasive.

Applicants' argue that, "both applicant and Kahn demonstrated loss of GPV gene expression in the homozygous mice"; "Applicants contend that the experimentation Kahn performed to examine the phenotype of that GPV deficient mouse led to insufficient data to conclusively determine the phenotype"; "A review of comparing the experimental results of Applicants and Kahn leads Applicants to argue that the phenotype produced by Kahn is the same." See pages 7-8 of applicants' traversal.

With respect to applicants' argument that, "both applicant and Kahn demonstrated loss of GPV gene expression in the homozygous mice," the argument is not

found persuasive because the loss of GPV gene expression in the homozygous mice is not the basis of the 112 first paragraph rejection. The rejection is based on the different phenotype observed by Kahn compared to the phenotype observed in the instant specification. The rejection is further based on how the claims embrace both phenotypes and the specification fails to provide sufficient guidance or evidence to use both GP V deficient mice. The claims embrace a transgenic mouse comprising a modified GP V gene. Without reciting the essential materials and methods, in particular when the modification of the GP V gene must occur at a level resulting in a corresponding phenotype (e.g., mouse has decreased bleeding time) that would distinguished it from a +/- or -/- GP V deficient transgenic mouse. MPEP 2164.08(c) recites, "A feature which is taught as critical in a specification and is not recited in the claims should result in a rejection of such claim under the enablement provision section of 35 U.S.C. 112." This is the case here. The construct used in the specification is different than the construct used by Kahn. The phenotype (decreased bleeding time) observed in the as-filed specification is different then the phenotype observed by Kahn (bleeding time indistinguishable from a wild-type mice). The construct used in the specification is required for one skilled in the art to practice the claimed invention and the body of the claims does not recite the construct used to produce the GP V deficient transgenic mouse, wherein said mouse has a decreased bleeding time.

With respect to the arguments that, "A review of comparing the experimental results of Applicants and Kahn leads Applicants to argue that the phenotype produced by Kahn is the same," appears to conflict with applicants response filed on 5/30/02 because in that response, applicants stated that, "Kahn's results may be attributable to the use of

different reagents and methodologies." See pages 6-7. Furthermore, applicants' arguments that, "experimentation performed to examine the phenotype of that GPV deficient mouse led to insufficient data to conclusively determine the phenotype (see page 7)" and "A review of comparing the experimental results of Applicants and Kahn leads Applicants to argue that the phenotype produced by Kahn is the same" appear to contradict each other. Clarification is requested.

In response to applicant's argument that, "A review comparing the experimental results of applicants and Kahn leads applicants to argue that the phenotype produced by Kahn is the same," and "Applicants concluded no difference was detectable among phenotypes," the argument is not found persuasive because MPEP § 716.01(c) states:

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 8, 10, and 13, are indefinite because the term "wherein said mouse has a decreasing bleeding time" in the preamble does not give weight to the phenotype. The body of the claims do not fully and intrinsically set forth all of the limitations of the claimed invention because the steps in the body of the claims do not define the phenotype in the pre-amble.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is: said mouse has a decreased bleeding time compared to what, e.g., +/+ or +/- GP V mouse. The claim does not define what is being compared to determine that the mouse has a decreased bleeding time.

Response to Arguments

Applicant's arguments, see paper no., filed on 9/16/03, with respect to the 103(a) rejection have been fully considered and are persuasive. The rejection of claims 1, 3, 5, 8, 10, 23, 24, 26, and 27 has been withdrawn because of the amendment to the claims to recite, "said transgenic mouse has a decrease bleeding time (page 9)."

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635